09/720,326

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Err r Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 1 | BRS | L1 | 675 | 424/130.1.ccls. | USPAT; US-PGPUB | 2002/03/15 12:13 | | | 0 |
| 2 | BRS | L2 | 157 | 424/134.1.ccls. | USPAT; US-PGPUB | 2002/03/15 12:13 | | | 0 |
| 3 | BRS | L3 | 382 | 424/141.1.ccls. | USPAT; US-PGPUB | 2002/03/15 12:13 | | | 0 |
| 4 | BRS | L4 | 143 | 424/142.1.ccls. | USPAT; US-PGPUB | 2002/03/15 12:13 | | | 0 |
| 5 | BRS | L5 | 322 | 424/143.1.ccls. | USPAT; US-PGPUB | 2002/03/15 12:13 | | | 0 |
| 6 | BRS | L6 | 268 | 424/145.1.ccls. | USPAT; US-PGPUB | 2002/03/15 12:14 | | | 0 |
| 7 | BRS | L7 | 6033 | 514/12-19.ccls. | USPAT; US-PGPUB | 2002/03/15 12:14 | | | 0 |
| 8 | BRS | L8 | 7293 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | USPAT; US-PGPUB | 2002/03/15 12:15 | | | 0 |
| 9 | BRS | L9 | 104 | parathyroid adj hormone adj related adj protein | USPAT; US-PGPUB | 2002/03/15 12:15 | | | 0 |
| 10 | BRS | L12 | 150 | pthrp | USPAT; US-PGPUB | 2002/03/15 12:16 | | | 0 |
| 11 | BRS | L13 | 189 | 9 or 12 | USPAT; US-PGPUB | 2002/03/15 12:16 | | | 0 |
| 12 | BRS | L14 | 57196 | antibody or antibodies | USPAT; US-PGPUB | 2002/03/15 12:16 | | | 0 |
| 13 | BRS | L16 | 18 | 13 same 14 | USPAT; US-PGPUB | 2002/03/15 12:16 | | | 0 |

09/720,326

| Set | Items | Description |
|---|---|---|
| S1 | 24512 | AU="SATO K" |
| S2 | 5038 | AU="SATO K." |
| S3 | 192 | AU="TSUNENARI T" OR AU="TSUNENARI T." OR AU="TSUNENARI TOSHIAKI" OR AU="TSUNENARI TOSHIAKI CHUGAI SEIYAKU K K" OR AU="TSUNENARI TOSHIAKI CHUGAI SEIYAKU KABUSHIKI" OR AU="TSUNENARI TOSHIYASU" |
| S4 | 29728 | S1 OR S2 OR S3 |
| S5 | 468 | HYPERCALCEMIC(W)CRISIS |
| S6 | 10275 | PARATHYROID(W)HORMONE(W)RELATED(W)PROTEIN |
| S7 | 10903 | PTHRP |
| S8 | 14917 | S6 OR S7 |
| S9 | 6612718 | MALIGNAN? OR CANCER? ? OR TUMOR? ? OR TUMOUR? ? OR NEOPLAS? |
| S10 | 3019014 | ANTIBODY OR ANTIBODIES |
| S11 | 153938 | CHIMERIC |
| S12 | 25089088 | HUMANIZED OR HUMAN |
| S13 | 1117 | S8(S)S10 |
| S14 | 22 | S4 AND S13 |
| S15 | 8 | S14 NOT PY>1998 |
| S16 | 2 | RD (unique items) |
| S17 | 0 | S S13 AND S5 |
| S18 | 15 | S5 AND S6 AND S9 |
| S19 | 12 | S18 NOT PY>1998 |
| S20 | 6 | RD (unique items) |
| S21 | 750 | S13 AND S9 |
| S22 | 77 | S21 AND S11 |
| S23 | 621 | S21 AND S12 |
| S24 | 624 | S22 OR S23 |
| S25 | 437 | S24 NOT PY>1998 |
| S26 | 179 | RD (unique items) |
| S27 | 7380779 | THERAPY OR THERAPEUTIC OR MEDICAMENT |
| S28 | 52 | S26 AND S27 |
| S29 | 127 | S26 NOT S28 |
| S30 | 10 | 23(W)57(W)137(W)1 |
| S31 | 0 | 23571371 |
| S32 | 10 | S30 OR S31 |
| S33 | 0 | S32 AND S26 |
| S34 | 10 | S10 AND S30 |
| S35 | 2 | S34 NOT PY>1998 |
| S36 | 2 | RD (unique items) |

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**16/3,AB/1 (Item 1 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

09355440 97289447 PMID: 9144352

**Synovial fluids from patients with osteoarthritis and rheumatoid arthritis contain high levels of parathyroid hormone-related peptide.**

Kohno H; Shigeno C; Kasai R; Akiyama H; Iida H; Tsuboyama T; **Sato K** ; Konishi J; Nakamura T

Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Sakyo, Japan.

Journal of bone and mineral research (UNITED STATES) May 1997, 12 (5) p847-54, ISSN 0884-0431 Journal Code: 130

Languages: ENGLISH

Document type: Clinical Trial; Controlled Clinical Trial; Journal Article

Record type: Completed

High levels of immunoreactive and biologically active parathyroid hormone-related peptide ( **PTHrP** ) were detected in synovial fluids from patients with osteoarthritis (OA) and rheumatoid arthritis (RA). The levels of **PTHrP** immunoreactivity in synovial fluids, measured by a two-site immunoradiometric assay (IRMA) which detects hPTHrP(1-72) or longer peptides and a radioimmunoassay (RIA) specific to the carboxy-terminal portion of hPTHrP, were 3.2 +/- 0.3 pmol of hPTHrP(1-86)/l and 61 +/- 7.0 pmol of hPTHrP(109-141)/l in OA patients (mean +/- SE, n = 23), and 4.8 +/- 0.8 pmol of hPTHrP(1-86)/l and 164 +/- 30 pmol of hPTHrP(109-141)/l in RA patients (n = 26). Synovial fluid **PTHrP** levels distributed above the normal plasma reference ranges in each assay (0.7-2.6 pmol of hPTHrP(1-86)/l; 16-60.6 pmol of hPTHrP(109-141)/l). After concentration using sequential cation-exchange and reverse-phase chromatography, synovial fluid exhibited the activity that stimulated cyclic adenosine monophosphate (cAMP) accumulation in osteoblastic ROS 17/2.8 cells expressing PTH/ **PTHrP** receptors. The cAMP accumulation activity in synovial fluid was sensitive to coincubation with excess hPTHrP(3-40), a PTH/ **PTHrP** receptor antagonist, and was completely neutralized by preincubation with a monoclonal **antibody** specific to hPTHrP but not PTH. Immunohistochemical analysis of RA synovium revealed that **PTHrP** was localized in fibroblast-like cells in the synovial pannus invading articular cartilage. Our data show that **PTHrP** is produced locally by the diseased synovial tissue and released into synovial fluid at high concentrations, allowing us to hypothesize that **PTHrP** plays a novel role as a paracrine/autocrine factor in the pathology of OA and RA.

**16/3,AB/2 (Item 2 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

07142192 93355917 PMID: 8352067

**Passive immunization with anti-** parathyroid hormone - related protein **monoclonal** antibody **markedly prolongs survival time of hypercalcemic nude mice bearing transplanted human** PTHrP **-producing tumors.**

**Sato K** ; Yamakawa Y; Shizume K; Satoh T; Nohtomi K; Demura H; Akatsu T; Nagata N; Kasahara T; Ohkawa H; et al

Institute of Clinical Endocrinology, Tokyo Women's Medical College, Japan.

Journal of bone and mineral research (UNITED STATES) Jul 1993, 8 (7) p849-60, ISSN 0884-0431 Journal Code: 130

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Malignancy-associated hypercalcemia is mainly caused by excessive production of parathyroid hormone-related protein ( **PTHrP** ) by the tumor. Using anti- **PTHrP** -(1-34) monoclonal murine **antibody** (anti- **PTHrP** MoAb), we studied whether repeated injection of the homologous **antibody** would continuously decrease the serum calcium concentration in hypercalcemic nude mice bearing transplanted human **PTHrP** -producing tumors, leading to prolongation of their survival time. Daily SC injections of anti- **PTHrP**

MoAb decreased the serum calcium concentration almost to within the normal range in nude mice bearing transplanted human **PTHrP** -producing tumors (T3M-1, EC-GI, PC-3, and FA-6) but not in a nude mouse bearing a transplanted parathyroid carcinoma. The **antibody** did not affect FA-6 tumor growth either in vitro or in vivo. Pancreatic carcinoma cells (FA-6), which caused the most severe hypercalcemia, were inoculated into 6-week-old nude mice. When severe hypercalcemia (approximately 19 mg/dl) had developed, daily SC injection of anti- **PTHrP** MoAb was started. Within 18 days of this time point, all untreated tumor-bearing mice (n = 10) died of hypercalcemia and cachexia, whereas all the treated mice (n = 10) showed an increase in body weight and survived for at least 25 days. Histologic examination of the treated mice revealed a marked decrease in osteoclastic bone resorption, without toxicologic findings in the kidney and liver. These results suggest that passive immunization against **PTHrP** can continuously ameliorate the hypercalcemia and markedly prolong the survival time of severely hypercalcemic, tumor-bearing mice. If a human monoclonal **antibody** against **PTHrP** -(1-34) could be developed, then passive immunization would be potentially one of the most effective therapies for patients with malignancy-associated hypercalcemia due to excessive production of **PTHrP** .
?

**20/3,AB/2 (Item 2 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

08014635 94281729 PMID: 8012094
**Increased 1,25-(OH)2D2 concentration in a patient with** malignancy **-associated hypercalcemia receiving intravenous hyperalimentation inadvertently supplemented with vitamin D2.**
Sato K; Imaki T; Toraya S; Demura H; Tanaka M; Kasajima T; Takeuchi A; Kobayashi T
Department of Medicine, Tokyo Women's Medical College.
Internal medicine (JAPAN) Nov 1993, 32 (11) p886-90, ISSN 0918-2918 Journal Code: BD6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A 55-year-old patient with **hypercalcemic crisis** due to gastric carcinoma with bone marrow metastasis was treated with bisphosphonate (pamidronate) and calcitonin. Urinary excretion of **parathyroid hormone - related protein** (PTHrP) was increased. When normocalcemia had been attained, intravenous hyperalimentation was started, in which 1,000 U vitamin D2 was inadvertently supplemented on days 5-18, On days 15-18, hypercalcemia rapidly recurred, accompanied by markedly increased serum levels of 25-OHD2 (9.1 ng/dl) and 1,25-(OH)2D2 (161 pg/ml). This clinical course suggests that PTHrP, like PTH, stimulated 1 alpha-hydroxylase activity and produced excessive 1,25-(OH)2D2. Vitamin D should not be administered to patients with **malignancy** -associated hypercalcemia, particularly that due to PTHrP-producing **tumors** .

**20/3,AB/3 (Item 3 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

07671951 93108624 PMID: 1469794
**Urinary excretion of** parathyroid hormone - related protein **as a predictor of hypercalcemia in patients with adult T-cell leukemia.**
Imamura H; Koreeda Y; Okadome T; Tara M; Niina K; Shizume K; Ohsumi K; Sato K
Internal Medicine, Kagoshima Municipal Hospital.
Japanese journal of clinical oncology (JAPAN) Oct 1992, 22 (5) p325-30, ISSN 0368-2811 Journal Code: KIN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Hypercalcemia with adult T-cell leukemia (ATL) is chiefly caused by an excessive production by **tumor** cells of **parathyroid hormone - related protein** (PTHrP). We have previously reported hypercalcemic patients with solid **tumors** to excrete a large amount of the C-terminal fragments of PTHrP (C-PTHrP) into their urine. To elucidate whether PTHrP production correlates with or predicts the development of hypercalcemia, we studied the urinary excretion of C-PTHrP in 36 ATL patients. The urinary excretion of C-PTHrP was in the normal range (< 0.40 nmol equivalent to PTHrP (109-141)/g creatinine) in HTLV-1-positive carriers (n 3), ATL patients in complete remission (n 2) and chronic type ATL patients (n 2). It was marginally increased in seven patients in partial remission, and gradually increased as the disease progressed. In 20 patients who died without or with hypercalcemia, it was increased to 1.98 +/- 0.69 (n 9) and 7.6 +/- 2.1 nmol/g creatinine (mean +/- SD, n 11, P < 0.01), respectively. Urinary C-PTHrP excretion was significantly correlated with serum calcium and LDH levels as well as with CD25-positive cells in the peripheral blood. In four patients whose urinary excretion had been serially determined, it increased prior to the development of hypercalcemia. The findings suggest the urinary excretion of C-PTHrP to be of use as a predictor of the development of hypercalcemia in ATL patients. In ATL patients whose urinary excretion of C-PTHrP is progressively increasing, the serum calcium concentration should be carefully monitored to prevent **hypercalcemic crisis** .
?ds

**28/3,AB/1 (Item 1 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

09808448 98280137 PMID: 9617151
**[A case of PTH related protein-producing large cell carcinoma of the lung]**
Katakami N
Department of Pulmonary Diseases, Kobe City General Hospital, Japan.
Nihon Kokyuki Gakkai zasshi (JAPAN) Feb 1998, 36 (2) p203-7, ISSN 1343-3490 Journal Code: C33
Languages: JAPANESE
Document type: Journal Article
Record type: Completed
A 41-year old woman with lung **cancer** was admitted to our hospital with constipation, lumbago and paraplegia. Her serum calcium level was 13.9 mg/dl. She expired on the 33rd hospital day despite vigorous fluid and supportive **therapy** . An autopsy was performed 1 hour later. The cause of death was rupture of the sigmoid colon and panperitonitis. To evaluate the etiology underlying the symptomatic hypercalcemia in the autopsied lung, we measured serum and **tumor** tissue concentrations of PTH-related protein ( **PTHrP** ) by radioimmunoassay using a specific **antibody** against **human PTHrP** (1-34), and performed immunohistochemical staining by the peroxidase-anti-peroxidase method with the same **PTHrP** antiserum. Northern blot analysis was also performed to detect messenger RNA in **cancer** tissue. All of these tests were positive for **PTHrP** . To the best of our knowledge, this is the first reported autopsied case demonstrated to be a **PTHrP** -producing large cell lung **cancer** by molecular biological methods.

**28/3,AB/2 (Item 2 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

08628257 96044381 PMID: 7565443
**A case of acute lymphoblastic leukemia accompanied with the production of parathyroid hormone-related protein.**
Harutsumi M; Akazai A; Kitamura T; Manki A; Tanaka H; Oda M; Seino Y
Department of Pediatrics, Okayama University Medical School, Japan.
Mineral and electrolyte metabolism (SWITZERLAND) 1995, 21 (1-3) p171-6, ISSN 0378-0392 Journal Code: M9Z
Languages: ENGLISH
Document type: Journal Article; Review; Review of Reported Cases
Record type: Completed
Hypercalcemia accompanied with **malignant tumors** is generally classified into two categories, namely with or without bone metastasis. As for the latter, bone resorption-stimulating factors produced by **tumor** cells, such as **parathyroid hormone - related protein** ( **PTHrP** ), show hormone-like effects and promote a bone resorption. Many cases have been reported regarding the production of TPTHrP in adult T cell leukemia (ATL), but few have been reported with acute lymphoblastic leukemia (ALL). We report here a similar case with ALL. A 12-year-old male presented with fever, petechiae and thrombocytopenia, and was diagnosed as ALL. We started the induction **therapy** and confirmed complete remission. Later, he relapsed 3 times without symptoms apart from hypercalcemia at the beginning. Elevation of the serum calcium level followed by a rise of lymphoblastic cells was recognized. Bone metastasis was excluded since bone mineral density and serum mid region PTH were normal and no abnormal findings were noticed on X rays and 99mTc bone scintigraphy. However, his urinary **PTHrP** level was high, and his lymphoblastic cells staining immunocytochemically with the monoclonal **antibodies** against the C-terminal region of **PTHrP** showed a positively brownish color. Finally, he died of pulmonary aspergillosis. Hypercalcemia was not related to serum PTH or bone metastasis. ATL viral infection reported as a cause of **PTHrP** production was also excluded from several experimental data. Therefore, we concluded that lymphoblastic cells directly produced **PTHrP** , and that this **PTHrP** played an important role in the induction of hypercalcemia.

**28/3,AB/3 (Item 3 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

07142192 93355917 PMID: 8352067
**Passive immunization with anti-** parathyroid hormone - related protein **monoclonal** antibody **markedly prolongs survival time of hypercalcemic nude mice bearing transplanted** human PTHrP **-producing** tumors .
Sato K; Yamakawa Y; Shizume K; Satoh T; Nohtomi K; Demura H; Akatsu T; Nagata N; Kasahara T; Ohkawa H; et al
Institute of Clinical Endocrinology, Tokyo Women's Medical College, Japan.
Journal of bone and mineral research (UNITED STATES) Jul 1993, 8 (7) p849-60, ISSN 0884-0431 Journal Code: 130
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
**Malignancy** -associated hypercalcemia is mainly caused by excessive production of parathyroid hormone-related protein ( **PTHrP** ) by the **tumor** . Using anti- **PTHrP** -(1-34) monoclonal murine **antibody** (anti- **PTHrP** MoAb), we studied whether repeated injection of the homologous **antibody** would continuously decrease the serum calcium concentration in hypercalcemic nude mice bearing transplanted **human PTHrP** -producing **tumors** , leading to prolongation of their survival time. Daily SC injections of anti- **PTHrP** MoAb decreased the serum calcium concentration almost to within the normal range in nude mice bearing transplanted **human PTHrP** -producing **tumors** (T3M-1, EC-GI, PC-3, and FA-6) but not in a nude mouse bearing a transplanted parathyroid carcinoma. The **antibody** did not affect FA-6 **tumor** growth either in vitro or in vivo. Pancreatic carcinoma cells (FA-6), which caused the most severe hypercalcemia, were inoculated into 6-week-old nude mice. When severe hypercalcemia (approximately 19 mg/dl) had developed, daily SC injection of anti- **PTHrP** MoAb was started. Within 18 days of this time point, all untreated **tumor** -bearing mice (n = 10) died of hypercalcemia and cachexia, whereas all the treated mice (n = 10) showed an increase in body weight and survived for at least 25 days. Histologic examination of the treated mice revealed a marked decrease in osteoclastic bone resorption, without toxicologic findings in the kidney and liver. These results suggest that passive immunization against **PTHrP** can continuously ameliorate the hypercalcemia and markedly prolong the survival time of severely hypercalcemic, **tumor** -bearing mice. If a **human** monoclonal **antibody** against **PTHrP** -(1-34) could be developed, then passive immunization would be potentially one of the most effective therapies for patients with **malignancy** -associated hypercalcemia due to excessive production of **PTHrP** .

**28/3,AB/4 (Item 1 from file: 94)**
DIALOG(R)File 94:JICST-EPlus


03111445 JICST ACCESSION NUMBER: 97A0322730 FILE SEGMENT: JICST-E
**A Case of Squamous Cell Carcinoma (Scar** Cancer **) Associated with Hypercarcemia Which Seemed to be Derived from** Tumor **Cells.**
LEE S G (1); OTOSHI ERIKO (1); MIZUNO KANA (1); MATSUYOSHI NORIHISA (1); IMAMURA SADAO (1); OKAMURA YOSHINORI (2); KAMAOTO TOSHIYUKI (2); ADACHI TOSHIHIRO (2); HIAI HIROSHI (2)
(1) Kyoto Univ., Fac. of Med.; (2) Kyoto Univ., Graduate School
Hifuka Kiyo(Acta Dermatologica), 1997, VOL.92,NO.1, PAGE.7-11, FIG.4, TBL.1, REF.5
JOURNAL NUMBER: F0645AAE ISSN NO: 0065-1176 CODEN: HIKIA
UNIVERSAL DECIMAL CLASSIFICATION: 616.5-006 616.39
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication
ABSTRACT: We describe a case squamous cell carcinoma (scar **cancer** ) at the

right sole associated with hypercarcemia. During the clinical course, the serum carcium level elevated to be more than 10mg/dl and **parathyroid hormone related protein** (PTH-rP) level was high, although no bone metastasis was suggested. Immunohistochemical reaction with anti-PTH-rP monoclonal **antibody** was positive in the cytoplasm of carcinoma cells. We think that the hypercarcemia was related with SCC-derived PTH-rP. (author abst.)

**28/3,AB/6 (Item 3 from file: 94)**
DIALOG(R)File 94:JICST-EPlus


01257066 JICST ACCESSION NUMBER: 91A0205152 FILE SEGMENT: JICST-E
**Bone absorption and osteogenesis. Hypercalcemia with** malignant tumor .
ETO SUMIYA (1); WATANABE KEN'ICHI (1); NAKANO YOICHIRO (1)
(1) Univ. of Occupational and Environmental Health
Saishin Igaku, 1991, VOL.46,NO.2, PAGE.315-324, FIG.6, TBL.4, REF.27
JOURNAL NUMBER: Z0358AAR ISSN NO: 0370-8241 CODEN: SAIGA
UNIVERSAL DECIMAL CLASSIFICATION: 616-006-07
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Commentary
MEDIA TYPE: Printed Publication
ABSTRACT: Hypercalcemia is one of the most common complications in patients with **malignancy** and sometimes lethal. Sequential measurement of serum calcium levels is necessary to prevent the often observed overlooking of this serious paraneoplastic syndrome. This **neoplastic** syndrome is induced by cytokines as **PTHrP** or IL1 ect. which are secreted from **malignant** cells and stimulate bone resorption, and called HHM(humoral hypercalcemia of **malignancy** ). The sensitive RIA systems of serum **PTHrP** have been established and may be useful for the differential diagnosis of hypercalcemia. The most effective treatment for HHM is conservatively the combination of glucocorticoids and calcitonin. The treatments directly related to cytokines responsible for HHM are under investigations. Namely, the administration of biologically non-active PTHrPvPTH analogs, anti- **PTHrP** monoclonal **antibodies** or IL 4 which has very recently been proved to suppress bone resorption seemed to decrease the hypercalcemia induced in athymic mice bearing various **human malignant tumors** with hypercalcemia. (author abst.)

**28/3,AB/12 (Item 4 from file: 349)**
DIALOG(R)File 349:PCT FULLTEXT


00340278
**COMPOSITION TO AMELIORATE OSTEOLYSIS AND METASTASIS**
**PROCEDE VISANT A INHIBER L'OSTEOLYSE ET LES METASTASES**
Patent Applicant/Assignee:
XENOTECH INCORPORATED,
Inventor(s):
MUNDY Gregory R,
YONEDA Toshiyuki,
GUISE Theresa A,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9622790 A1 19960801
Application: WO 96US895 19960123 (PCT/WO US9600895)
Priority Application: US 95376359 19950123; US 95386361 19950209; US 95481088 19950606
Designated States: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AZ BY KG KZ RU TJ TM AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English

Fulltext Word Count: 15163

English Abstract
A therapeutically effective amount of an **antibody** for a compound selected from the group consisting of **PTHrp** , TGF'alpha', IL-1'alpha', IL-1'beta', IL-6, Lymphotoxin, TNF, PGE; 1,25 dihydroxy vitamin D3 and an antigenic fragment thereof used in the treatment of **cancer** metastasis to bone and **cancer** cell growth in bone as well as osteolysis and symptomatic sequelae thereof. An **antibody** immunoreactive with **parathyroid hormone - related protein** ( **PTHrp** ) is particularly preferred. **Antibodies** with **human** characteristics are included in the invention for application of the invention method to **human** subjects. Also, the **antibody** can be administered in an injectable formulation in combination with a therapeutically effective amount of a bisphosphonate or pyrophosphate having general structure formula (I), wherein X is a linking moiety allowing for the interconnection of the phosphonate groups, and pharmaceutically acceptable salts, hydrates and partial hydrates thereof. The **antibody** and bisphosphonate act synergistically in the treatment of **cancer** metastases to bone and symptomatic sequelae thereof and particularly as regards bone resorption.

French Abstract
Quantite efficace therapeutiquement d'un anticorps pour un compose selectionne a partir du groupe constitue par PTHrp, TGF'alpha', IL-1'alpha', IL-1'beta', IL-6, lymphotoxine, TNF, PGE, 1,25 dihydroxy vitamine D3 et un de ses fragments antigeniques utilises dans le traitement des metastases du **cancer** vers les os et de la croissance des cellules cancereuses dans l'os, ainsi que de l'osteolyse et de ses sequelles symptomatiques. Un anticorps presentant une reaction immune avec une proteine relative a l'hormone de parathyroide (PTHrp) est particulierement prefere. L'invention comprend egalement des anticorps possedant des caracteristiques humaines, permettant l'application du procede de l'invention a l'homme. L'anticorps peut etre administre sous forme injectable combinee a une quantite therapeutiquement efficace d'un bisphosphonate ou d'un pyrophosphate represente par la formule de structure generale (I): dans laquelle X represente une fraction de liaison permettant de relier les groupes phosphonate, ainsi que leurs sels, hydrates et hydrates partiels acceptables pharmaceutiquement. L'anticorps et le bisphosphonate exercent une action synergique dans le traitement des metastases du **cancer** vers l'os et de ses sequelles symptomatiques, particulierement en ce qui concerne la resorption osseuse.

**28/3,AB/14 (Item 6 from file: 349)**


00220367
**PARATHYROID HORMONE RECEPTOR AND DNA ENCODING SAME**
**RECEPTEUR D'HORMONE PARATHYROIDIENNE ET ADN CODANT CE RECEPTEUR**
Patent Applicant/Assignee:
THE GENERAL HOSPITAL CORPORATION OFFICE OF TECHNOLOGY AFFAIRS,
Inventor(s):
SEGRE Gino V,
KRONENBERG Henry M,
ABOU-SAMRA Abdul-Badi,
JUPPNER Harald,
POTTS John T Jr,
SCHIPANI Ernestina,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9217602 A1 19921015
Application: WO 92US2821 19920406 (PCT/WO US9202821)
Priority Application: US 91702 19910405; US 92475 19920406
Designated States: AT BE CA CH DE DK ES FR GB GR IT JP LU MC NL SE
Publication Language: English

Fulltext Word Count: 19809

English Abstract
DNA encoding a parathyroid hormone receptor; production and isolation of recombinant and synthetic parathyroid hormone receptor polypeptides and fragments; antibodies to parathyroid hormone receptors and receptor fragments; methods for screening candidate compounds for antagonistic or agonistic effects on parathyroid hormone receptor action; and diagnostic and **therapeutic** methods of these compounds are disclosed.

French Abstract
ADN codant un recepteur d'hormone parathyroidienne; production et isolation de polypeptides et de fragments synthetiques et de recombinaison de recepteurs d'hormone parathyroidienne; anticorps contre les recepteurs d'hormone parathyroidienne et les fragments de recepteurs; procede de criblage de composes susceptibles de presenter des effets antagonistes ou agonistes sur l'action des recepteurs d'hormone parathyroidienne; et procedes diagnostiques et therapeutiques utilisant ces composes.

**28/3,AB/15 (Item 7 from file: 349)**
DIALOG(R)File 349:PCT FULLTEXT


00213295
**COMPOUNDS AND COMPOSITIONS WHICH INHIBIT BONE RESORPTION**
**COMPOSE ET COMPOSITIONS D'INHIBITION DE LA RESORPTION OSSEUSE**
Patent Applicant/Assignee:
THE UNIVERSITY OF MELBOURNE,
GENENTECH INC,
KEMP Bruce E,
NICHOLSON Geoffrey Charles,
MARTIN Thomas J,
FENTON Anna Jane,
HAMMONDS R Glenn,
Inventor(s):
KEMP Bruce E,
NICHOLSON Geoffrey Charles,
MARTIN Thomas J,
FENTON Anna Jane,
HAMMONDS R Glenn,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9210511 A1 19920625
Application: WO 91AU580 19911213 (PCT/WO AU9100580)
Priority Application: AU 903879 19901213; AU 919567 19911119
Designated States: AT AT AU BB BE BF BG BJ BR CA CF CG CH CH CI CM DE DE DK DK ES ES FI FR GA GB GB GN GR HU IT JP KP KR LK LU LU MC MG ML MR MW NL NL NO PL RO SD SE SE SN SU TD TG US
Publication Language: English
Fulltext Word Count: 10658

English Abstract
Carboxyl terminal fragments of PTHrP also known by the name adenylate cyclase stimulating factor [ACSF] and bone releasing factor [BRF] are shown to possess bone resorption inhibitory activity which is an opposite activity to that embodied by the complete PTHrP sequence and N-terminal fragments thereof. There is described compounds having bone resorption inhibitory activity which comprise carboxy terminal fragment of PTHrP consisting of at least amino acids 107-111 of PTHrP, or a derivative thereof. Methods for the inhibition of bone resorption, and methods for the treatment of diseases characterised by excess bone resorption are also described, which methods comprise administering to a subject in need of such treatment a bone resorption inhibitory effective amount of a carboxy terminal fragment of PTHrP consisting of at least amino acids 107-111 of PTHrP or a derivative thereof optionally in association with a

pharmaceutically acceptable carrier or excipient.

French Abstract

On a demontre que des fragments a terminaison carboxy de PTHrP, connus egalement sous le nom de facteur de stimulation d'adenyl-cyclase (ACSF) et de facteur de liberation osseuse (BRF), presentent une activite d'inhibition de la resorption osseuse, qui est une activite opposee a celle de la sequence PTHrP complete et des fragments N-terminaux de celle-ci. On decrit des composes presentant une activite d'inhibition de la resorption osseuse et comprenant un fragment a terminaison carboxy de PTHrP se composant d'au moins des acides amines 107-111 de PTHrP, ou d'un derive de ceux-ci. On decrit egalement des procedes d'inhibition de la resorption osseuse ainsi que des procedes de traitement de maladies se caracterisant par une resorption osseuse excessive. Ces procedes consistent a administrer au patient necessitant un tel traitement une quantite suffisante et inhibant efficacement la resorption osseuse de fragments a terminaison carboxy de PTHrP se composant au moins des acides amines 107-111 de PTHrP ou d'un derive de ceux-ci, eventuellement en conjonction avec un vecteur ou un excipient acceptable en pharmacologie.

**28/3,AB/34 (Item 19 from file: 654)**

DIALOG(R)File 654:US PAT.FULL.



02682503

Utility

**THERAPEUTIC** SEPSIS TREATMENT USING ANTAGONISTS TO PTHRP

[ Administering to reduce or delay some of toxic effects of endotoxins or cytokines]

PATENT NO.: 5,660,826
ISSUED: August 26, 1997 (19970826)
INVENTOR(s): Grunfield, Carl, San Francisco, CA (California), US (United States of America)
Funk, Janet, San Francisco, CA (California), US (United States of America)
Feingold, Kenneth R., San Rafael, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-477,348
FILED: June 06, 1995 (19950606)

This invention was made with Government support under Grant No. DK 47846 awarded by the National Institutes of Health and funds from the Research Service of the Department of Veterans' Affairs. The Government has certain rights in this invention.

FULL TEXT: 412 lines

ABSTRACT

Methods and compositions are provided for the treatment or prophylaxis of systematic inflammatory response syndrome by administering an antagonist to **parathyroid hormone - related protein** , such as **antibodies** to **PTHrP** .

**28/3,AB/51 (Item 36 from file: 654)**

DIALOG(R)File 654:US PAT.FULL.



02225824

Utility

PHARMACEUTICAL COMPOSITIONS FOR TREATING BONE DISORDERS
[In patients suffering from **malignant tumors** , interleukin-4]

PATENT NO.: 5,246,700
ISSUED: September 21, 1993 (19930921)
INVENTOR(s): Yamaguchi, Ken, Tokyo, JP (Japan)
Nagasaki, Koichi, Tokyo, JP (Japan)
Eto, Sumiya, Kitakyushu, JP (Japan)
ASSIGNEE(s): Tonen Corporation, (A Non-U.S. Company or Corporation ), Tokyo, JP (Japan)
[Assignee Code(s): 84908]
EXTRA INFO: Expired, effective September 21, 2001 (20010921), recorded in O.G. of November 27, 2001 (20011127)
APPL. NO.: 7-791,386
FILED: November 14, 1991 (19911114)
PRIORITY: 3-173355, JP (Japan), June 19, 1991 (19910619)

FULL TEXT: 210 lines

ABSTRACT

A composition for treating bone disorder or hypercalcemia of patients suffering from **malignant tumors** is disclosed. The composition of the present invention comprises an effective amount of interleukin-4 in a pharmaceutically acceptable carrier.

**28/3,AB/52 (Item 37 from file: 654)**
DIALOG(R)File 654:US PAT.FULL.


02191496
Utility
MONOCLONAL ANTIBODIES RECOGNIZING PARATHYROID HORMONE-LIKE PROTEIN
[For diagnosis and treatment of humoral hypercalcemia]

PATENT NO.: 5,217,896
ISSUED: June 08, 1993 (19930608)
INVENTOR(s): Kramer, Steven P., Kew Gardens, NY (New York), US (United States of America)
Valenzuela, David M., Franklin Square, NY (New York), US (United States of America)
Reynolds, Jr. Frederick H., Syosset, NY (New York), US (United States of America)
Sorvillo, John M., Merrick, NY (New York), US (United States of America)
ASSIGNEE(s): Oncogene Science, Inc , (A U.S. Company or Corporation ), Uniondale, NY (New York), US (United States of America)
[Assignee Code(s): 30230]
EXTRA INFO: Assignment transaction [Reassigned], recorded August 30, 1999 (19990830)
APPL. NO.: 7-292,263
FILED: December 30, 1988 (19881230)

FULL TEXT: 1220 lines

ABSTRACT

This invention provides a monoclonal antibody which specifically forms a complex with amino acids 1-87 of PTHLP which does not form a complex with amino acids 1-34 of PTHLP, and which forms a complex with the epitope to which any of the monoclonal antibodies produced by the hybridomas 212-10.7, (ATCC Accession No. HB9930), 199-999 (ATCC Accession No. HB9929), 199-278 (ATCC Accession No. HB9931), is directed.

This invention further provides methods of detecting PTHLP and of diagnosing and treating humoral hypercalcemia of **malignancy** .

**29/3,AB/1 (Item 1 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

10011641 98284978 PMID: 9623520
**Hypercalcemia due to parathyroid hormone-related protein secretion by melanoma.**
Yeung SC; Eton O; Burton DW; Deftos LJ; Vassilopoulou-Sellin R; Gagel RF
Division of Endocrinology, Department of Medicine, Baylor College of Medicine, Houston, Tex, USA.
Hormone research (SWITZERLAND) 1998, 49 (6) p288-91, ISSN 0301-0163 Journal Code: GBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
About 1-2% of melanoma patients develop hypercalcemia. We report hypercalcemia without bone metastasis in a 46-year-old woman with advanced melanoma. The hypercalcemia was associated with elevated serum **parathyroid hormone - related protein** ( **PTHrP** ) levels. An even higher concentration (10 times the serum level) in pleural effusion caused by pleural metastases implied that the source of the increased circulating **PTHrP** was the melanoma. Immunohistochemical staining of paraffin sections, performed using a monoclonal **antibody** (9H7) against the peptide sequence 109-141 of **human PTHrP** , detected **PTHrP** in the cytoplasm and nucleoli of melanoma cells in an autopsy specimen but not in specimens from this patient prior to onset of hypercalcemia. Considering the evidence, it is very likely that **PTHrP** production by melanoma caused hypercalcemia in this patient.

**29/3,AB/14 (Item 14 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

09520408 97117236 PMID: 8958305
**Enhanced expression of parathyroid hormone-related protein in prostate cancer as compared with benign prostatic hyperplasia.**
Asadi F; Farraj M; Sharifi R; Malakouti S; Antar S; Kukreja S
Department of Medicine, VA West Side Medical Center, Chicago, Illinois 60612, USA.
Human pathology (UNITED STATES) Dec 1996, 27 (12) p1319-23, ISSN 0046-8177 Journal Code: GEC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Parathyroid hormone-related protein ( **PTHrP** ) has been shown to be the primary factor responsible for humoral hypercalcemia of **malignancy** . Recently **PTHrP** has been shown to be an early-response gene that may be involved in cellular proliferation or differentiation. In addition, **PTHrP** has been implicated in the pathogenesis of bone metastases. Bone metastases are a significant complication in patients with prostate **cancer** . We compared the expression of **PTHrP** by immunohistochemical staining using a monoclonal **antibody** directed against epitope between amino acids [53-64] in benign prostatic hyperplasia (BPH) with that in various stages of prostate **cancer** . Tissue sections were obtained on formalin-fixed paraffin-embedded blocks from BPH, well-differentiated prostate **cancer** , poorly differentiated prostate **cancer** , lymph node metastases (n = 15 each), and normal prostate (n = 2). In the normal prostate tissue there was no staining observed. In BPH, 13 of 15 tissue samples were positive for **PTHrP** immunoreactivity. An average of 33% of the cells stained positive with 1+ intensity. All samples from prostate **cancer** stained positive for **PTHrP** . In the samples from well-differentiated prostate **cancer** , an average of 87% of cells stained positive for **PTHrP** , whereas 100% of cells were positive in poorly differentiated and metastatic **tumors** . The intensity of staining was 3+ in well-differentiated **tumors** and 4+ in poorly differentiated **tumors** . Therefore, the expression of **PTHrP** is enhanced in prostate **cancer** as compared with BPH and is greater in poorly

differentiated carcinoma as compared with the well-differentiated **tumors** . The role of **PTHrP** in the pathogenesis of prostate **cancer** deserves further study.

**29/3,AB/21 (Item 21 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

09046029 97099243 PMID: 8943820
**Expression of parathyroid hormone (PTH)-related peptide (PTHrP) and PTH/PTHrP receptor in giant cell** tumour **of tendon sheath.**
Nakashima M; Ito M; Ohtsuru A; Alipov GK; Matsuzaki S; Nakayama T; Yamashita S; Sekine I
Department of Pathology and Cell Physiology, Atomic Disease Institute, Nagasaki University School of Medicine, Nagasaki, Japan.
Journal of pathology (ENGLAND) Sep 1996, 180 (1) p80-4, ISSN 0022-3417 Journal Code: JLB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The giant cell **tumour** of tendon sheath (GCTTS) is mainly composed of mononucleated stromal cells (SC) and multinucleated giant cells (GC), so-called osteoclast-like GC. It is thought that GC are derived from SC, but their precise relationship is not fully understood. Parathyroid hormone (PTH)-related peptide ( **PTHrP** ) is now considered to be a cytokine for cell differentiation, which may stimulate osteoclast-like cell formation in haematopoietic cells. Five cases of GCTTS were evaluated immunohistochemically, using a variety of **antibodies** against **PTHrP** , PTH/ **PTHrP** receptor, KP-1 as a histiocytic phenotypic antigen, fibronectin as a fibroblastic phenotypic antigen, and proliferating cell nuclear antigen (PCNA). In situ hybridization and immunohistochemistry revealed that in all cases both SC and GC expressed **PTHrP** . PTH/ **PTHrP** receptor was observed only in histiocytic SC and GC, but not in fibroblastic SC. Almost all GC showed histiocytic features. PCNA immunoreactivity was detected only in the nuclei of SC, and not in GC. Moreover, SC with PTH/ **PTHrP** receptor immunoreactivity were negative for PCNA. These results suggest that GC are derived from histiocytic SC expressing PTH/ **PTHrP** receptor and losing proliferative activity in the process of transition from mononuclear to multinucleated. **PTHrP** produced by SC and GC may be involved in the formation of osteoclast-like cells in GCTTS by acting in an autocrine/paracrine fashion.

**29/3,AB/23 (Item 23 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

09008054 96430820 PMID: 8833902
**Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of** human **breast** cancer **-mediated osteolysis.**
Guise TA; Yin JJ; Taylor SD; Kumagai Y; Dallas M; Boyce BF; Yoneda T; Mundy GR
Department of Medicine, University of Texas Health Science Center at San Antonio, 78284, USA.
Journal of clinical investigation (UNITED STATES) Oct 1 1996, 98 (7) p1544-9, ISSN 0021-9738 Journal Code: HS7
Contract/Grant No.: AR-01899, AR, NIAMS; CA-40035, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Breast **cancer** almost invariably metastasizes to bone in patients with advanced disease and causes local osteolysis. Much of the morbidity of advanced breast **cancer** is a consequence of this process. Despite the importance of the problem, little is known of the pathophysiology of local osteolysis in the skeleton or its prevention and treatment. Observations in patients with bone metastases suggest that breast **cancer** cells in bone express parathyroid hormone-related protein ( **PTHrP** ) more frequently than

in soft tissue sites of metastasis or in the primary tumor . Thus, the role of **PTHrP** in the causation of breast **cancer** metastases in bone was examined using **human** breast **cancer** cell lines. Four of eight established **human** breast **cancer** cell lines expressed **PTHrP** and one of these cell lines, MDA-MB-231, was studied in detail using an in vivo model of osteolytic metastases. Mice inoculated with MDA-MB-231 cells developed osteolytic bone metastasis without hypercalcemia or increased plasma **PTHrP** concentrations. **PTHrP** concentrations in bone marrow plasma from femurs affected with osteolytic lesions were increased 2.5-fold over corresponding plasma **PTHrP** concentrations. In a separate experiment, mice were treated with either a monoclonal **antibody** directed against **PTHrP** (1-34), control IgG, or nothing before **tumor** inoculation with MDA-MB-231 and twice per week for 26 d. Total area of osteolytic lesions was significantly lower in mice treated with **PTHrP** **antibodies** compared with mice receiving control IgG or no treatment. Histomorphometric analysis of bone revealed decreased osteoclast number per millimeter of **tumor** /bone interface and increased bone area, as well as decreased **tumor** area, in **tumor** -bearing animals treated with **PTHrP** **antibodies** compared with respective controls. These results indicate that **tumor** -produced **PTHrP** can cause local bone destruction in breast **cancer** metastatic to bone, even in the absence of hypercalcemia or increased circulating plasma concentrations of **PTHrP** . Thus, **PTHrP** may have an important pathogenetic role in the establishment of osteolytic bone lesions in breast **cancer** . Neutralizing **antibodies** to **PTHrP** may reduce the development of destructive bone lesions as well as the growth of **tumor** cells in bone.

**29/3,AB/39 (Item 39 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

08329772 95131119 PMID: 7829996
**Regulation of parathyroid hormone-related protein production in a** human **lung squamous cell carcinoma line.**
Rizzoli R; Feyen JH; Grau G; Wohlwend A; Sappino AP; Bonjour JP
Department of Medicine, University Hospital, Geneva, Switzerland.
Journal of endocrinology (ENGLAND) Nov 1994, 143 (2) p333-41, ISSN 0022-0795 Journal Code: I1J
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The synthesis and release of **parathyroid** **hormone** - **related** **protein** ( **PTHrP** ) could be influenced in a paracrine or autocrine manner by substances present around or inside **tumours** , such as bone or stromal cell-derived cytokines, factors produced by the **tumour** itself or by peritumoural inflammatory cells. We investigated the effects of various cytokines known to be synthesized by osteoblasts, stromal cells, leucocytes or **cancer** cells, on **PTHrP** production by the **human** lung squamous cell carcinoma line BEN. The influence of **tumour** necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) was studied, and compared with those of insulin-like growth factors-I and -II (IGF-I, IGF-II), or macrophage- or granulocyte-macrophage colony-stimulating factors (M-CSF, GM-CSF). TNF-alpha caused a 1.9 +/- 0.1-fold increase in immunoreactive **PTHrP** production, which was maximal by 24 h of incubation. IL-6 caused a 2.3 +/- 0.2-fold increase, which was maximal by 16 h. These effects, which were time- and concentration-dependent, were blocked by monoclonal **antibodies** raised against the corresponding cytokine. An increase of **PTHrP** mRNA was found in IL-6-treated cells. IGF-I and IGF-II increased **PTHrP** production by 2.0 +/- 0.3- and 2.3 +/- 0.1-fold respectively. Neither M-CSF nor GM-CSF altered **PTHrP** production up to 64 h of incubation. **PTHrP** production was not affected by varying extracellular calcium concentrations, but was decreased by incubation with 100 nmol/l dexamethasone.(ABSTRACT TRUNCATED AT 250 WORDS)

**29/3,AB/61 (Item 61 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

07259091 90232005 PMID: 2184438

**A novel parathyroid hormone-related protein: role in pathology and physiology.**

Martin TJ; Ebeling PR

University of Melbourne, Department of Medicine, Australia.

Progress in clinical and biological research (UNITED STATES) 1990, 332 p1-37, ISSN 0361-7742 Journal Code: PZ5

Languages: ENGLISH

Document type: Journal Article; Review; Review, Academic

Record type: Completed

Many factors, such as interleukin 1, TGF alpha, TNF alpha, and beta and prostaglandins, have been implicated in aetiological roles in HHM (Martin and Mundy, 1987). Much interest in the past has also centered upon the likelihood of ectopic secretion of PTH in this condition. We have purified a protein ( **PTHrP** ) implicated in HHM from a **human** lung **cancer** cell line (BEN). Full-length cDNA clones have been isolated and found to encode a prepropeptide of 36 amino acids and a mature protein of 141 amino acids. Eight of the first 13 amino acids were identical with **human** PTH, although antisera directed to the NH2-terminus of **PTHrP** do not recognize PTH; this homology is not maintained in the remainder of the molecule. **PTHrP** therefore represents a previously unrecognized hormone, possibly related to the PTH gene by a gene duplication mechanism. In support for this notion, the **PTHrP** gene has been localized to the short arm of chromosome 12; it is believed that chromosome 11, containing the PTH gene, and chromosome 12 are evolutionarily related. In addition, the **human** **PTHrP** gene has been isolated, characterized, and shown to have a similar intron/exon organization as the PTH gene. It is possible that the original ancestral gene is indeed the **PTHrP** gene; resolution of this question awaits studies in lower species. Peptides synthesized to the predicted protein sequence have enabled detailed structure-function studies that have identified NH2-terminal sequences to be responsible for the biological effects of the molecule. **Antibodies** raised against the various synthetic peptides have led to the immunohistochemical localization of **PTHrP** in many **human** squamous cell carcinomas as well as in subpopulation of keratinocytes of normal skin. The availability of these **antibodies** has opened the way for the development of a radioimmunoassay to detect **PTHrP** in the sera of **cancer** patients at risk of developing hypercalcemia. The recent characterization of **PTHrP** -like activity in the ovine fetus suggests some physiological function for **PTHrP** . It is possible that **PTHrP** , as the fetal counterpart of PTH, has the role of maintaining the maternal-fetal calcium gradient. The isolation and characterization of **PTHrP** has added to our understanding of the mechanisms of hypercalcemia, and may contribute to the understanding of other metabolic bone diseases such as osteoporosis and Paget's disease. Finally, and perhaps most importantly, **PTHrP** may play a hitherto unrecognized role in fetal calcium metabolism and in normal cell physiology.

**29/3,AB/68 (Item 68 from file: 155)**

DIALOG(R)File 155:MEDLINE(R)

06887589 93003406 PMID: 1390945

**Immunochemical characterisation of parathyroid hormone-related protein from** tumour **and non-** tumour **cells.**

Emly JF; Ratcliffe WA; Green E; Bowden SJ; Heath DA; Blight A; Hughes S; Ratcliffe JG

Wolfson Research Laboratories, Department of Clinical Chemistry, Queen Elizabeth Medical Centre, Birmingham, UK.

Biochimica et biophysica acta (NETHERLANDS) Oct 13 1992, 1180 (1) p58-64, ISSN 0006-3002 Journal Code: A0W

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The molecular forms of **parathyroid** **hormone - related** **protein** ( **PTHRP** ) in conditioned media from the BEN **human** lung **cancer** cell line,

rat parathyroid cells (PT-r) and **human** keratinocytes were studied by gel-filtration chromatography with assay of **PTHRP** by immunoassays and bioassay. Immunoreactivity (1-86 and 1-34) and bioactivity (1-34) in conditioned media eluted as a coincident major peak (approx. molecular mass 19-22 kDa) and there was evidence of amino-terminal species in the molecular mass range 10-16 kDa in BEN and keratinocyte media. Western blotting of **PTHRP** affinity purified by monoclonal **antibodies** directed at regions 1-34 or 37-67, identified a major species in all cell cytosols and media with an apparent molecular mass of 24-25 kDa, consistently slightly larger than recombinant **PTHRP** (1-141) (mobility of 21 kDa) which may represent an intact or native form of **PTHRP** . Additional amino-terminal species were identified in medium from keratinocytes (16 and 7 kDa), BEN cells (18 and 14 kDa) and PT-R cells (17 kDa), suggesting that processing occurs at the C-terminus and within the mid-region to form a range of amino-terminal fragments.

**29/3,AB/69 (Item 69 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

06832347 90203631 PMID: 1690780
**Production and characterisation of monoclonal antibodies to** parathyroid hormone - related protein .
Ratcliffe WA; Hughes S; Gilligan MG; Heath DA; Ratcliffe JG
Wolfson Research Laboratories, Department of Clinical Chemistry, Queen Elizabeth Medical Centre, Birmingham, U.K.
Journal of immunological methods (NETHERLANDS) Feb 20 1990, 127 (1) p109-16, ISSN 0022-1759 Journal Code: IFE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The production and characterisation of 17 monoclonal antibodies to **human parathyroid hormone - related protein** (PTH-rP) 1-34 is described. Five of the **antibodies** were shown to be of high avidity (Ka 4 X 10(10)-1.9 X 10(11) L/M) and able to detect 15-100 pg PTH-rP 1-34 per tube by RIA. None cross-reacted with PTH 1-34, and inhibition studies with peptide subfragments of PTH-rP 1-34 indicated that all recognise a central region extending from residues 9-18 to between residues 23 and 34. All **antibodies** tested cross-reacted with native PTH-rP in culture fluids from keratinocytes and squamous **cancer** cell lines and in **human** and bovine milk. The concentrations of PTH-rP 1-34 (ng/ml) in these fluids as determined by RIA were: keratinocytes 1-3, squamous **cancer** 0.2-2.5, **human** milk, up to 80. Selected **antibodies** coupled to Sepharose 4B were used to extract PTH-rP from biological fluids with high yields.

**29/3,AB/70 (Item 70 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

06786070 92036489 PMID: 1935171
**Parathyroid hormone-related protein: biochemistry and molecular biology.**
Martin TJ; Moseley JM; Gillespie MT
University of Melbourne, Department of Medicine, Australia.
Critical reviews in biochemistry and molecular biology (UNITED STATES) 1991, 26 (3-4) p377-95, ISSN 1040-9238 Journal Code: DTM
Languages: ENGLISH
Document type: Journal Article; Review; Review, Academic
Record type: Completed
This article critically reviews the current state of knowledge regarding the recently identified and cloned novel hormone **parathyroid hormone - related protein** ( **PTHrP** ). **PTHrP** is produced by **tumors** associated with the syndrome of humoral hypercalcemia of **malignancy** giving rise to the parathyroid hormone (PTH)-like symptoms characteristic of the syndrome. Areas that will be reviewed include identification, purification and cloning, localization, actions, and significance of **PTHrP** in **cancers** and normal physiology. The structure and regulation of the **PTHrP** gene

that may be ancestrally related to the PTH gene will also be discussed. Studies in vivo and in vitro with synthetic and recombinant **PTHrP** sequences and **antibodies** developed against them have established that the PTH-like actions of **PTHrP** are mediated via the N-terminal sequences, which show some limited sequence homology with PTH. Evidence for PTH and non-PTH-like actions of **PTHrP** in normal physiology, which implicate a role for **PTHrP** in fetal and neonatal development, is also presented.

**29/3,AB/71 (Item 71 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

06764988 91278852 PMID: 2056982
**PTH-related protein (PTHrP) in serum of patients with** tumor **hypercalcemia]**
PTH-related protein (PTHrP) im Serum von Patienten mit Tumorhyperkalzamie.
Scharla SH; Pecherstorfer M; Lempert UG; Minne HW; Sarrach M; Baumgartner G; Ziegler R
Innere Medizin I, Universitat Heidelberg.
Medizinische Klinik (GERMANY) Apr 15 1991, 86 (4) p186-9, ISSN 0723-5003 Journal Code: M9K
Languages: GERMAN
Document type: Journal Article
Record type: Completed
**Parathyroid hormone - related protein** ( **PTHrP** ) is a recently described hormone, that was isolated from **malignant tumors** . It shows many properties of parathyroid hormone (PTH) and is related to the pathogenesis of humoral hypercalcemia of **malignancy** . Therefore, we analyzed **PTHrP** in the sera of 30 patients with hypercalcemia of **malignancy** and compared the values with those obtained in patients with primary hyperparathyroidism, Paget's disease of bone, and normal subjects. **PTHrP** was quantitated with radioimmunoassay (RIA) using aminoterminal **antibodies** without and with chromatographical sample purification applying SEP-PAK C18 cartridges. Measurements of **PTHrP** without sample purification yielded high values in all patient groups. There was no differentiation between patient groups. However, quantitation of **PTHrP** after SEP-PAK C18 purification of the samples resulted in values above the normal range only in **tumour** patients. In 30 normal subjects **PTHrP** levels were 110 +/- 75 pg-eq/ml. Eight out of 30 patients with **malignant tumours** displayed **PTHrP** -concentrations above 335 pg-eq/ml. **PTHrP** levels in patients with primary hyperparathyroidism or Paget's disease of bone were within the normal range. **PTHrP** concentrations were not affected from renal function. We conclude, that determination of **PTHrP** after sample purification may contribute to the differential diagnosis of **malignant** disease.

**29/3,AB/77 (Item 77 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

06648603 90298869 PMID: 2361475
Tumor **resection and antibodies to** parathyroid hormone - related protein **cause similar changes on bone histomorphometry in hypercalcemia of** cancer **.**
Kukreja SC; Rosol TJ; Wimbiscus SA; Shevrin DH; Grill V; Barengolts EI; Martin TJ
Department of Medicine, Veterans Administration, Chicago, Illinois 60612.
Endocrinology (UNITED STATES) Jul 1990, 127 (1) p305-10, ISSN 0013-7227 Journal Code: EGZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Bone resorption is increased in both humoral hypercalcemia of **malignancy** (HHM) and primary hyperparathyroidism. On the other hand, bone formation parameters are increased in primary hyperparathyroidism and decreased in

IDS

**36/3,AB/1 (Item 1 from file: 357)**
DIALOG(R)File 357:Derwent Biotech Resource


0224799 DBA Accession No.: 98-06396 PATENT
**Chimeric and humanized** antibodies **against human parathormone-related peptides - chimeric** antibody **, humanized** antibody **and monoclonal** antibody **production by vector plasmid pUC19 expression in CHO and COS cell and hybridoma cell culture for hypercalcemia therapy**
AUTHOR: Sato K; Wakahara Y; Yabuta N
CORPORATE SOURCE: Tokyo, Japan.
PATENT ASSIGNEE: Chugai 1998
PATENT NUMBER: WO 9813388 PATENT DATE: 980402 WPI ACCESSION NO.: 98-230640 (9820)
PRIORITY APPLIC. NO.: JP 96214168 APPLIC. DATE: 960724
NATIONAL APPLIC. NO.: WO 97JP3382 APPLIC. DATE: 970924
LANGUAGE: JA
ABSTRACT: Humanized and chimeric **antibodies** which recognize human parathormone-related peptides (PTRP) are new and contain chimeric L and/or H chains in which the C region is of human origin and the L region is of mouse origin. Preferably, the V region is humanized containing framework regions of human origin and complementarity determining regions (CDRs) of mouse origin. Also claimed is: DNA coding for the **antibody** and its component parts; vectors containing the DNA; transformant hosts containing the vectors; and **antibody** production by transformant culture. The above may be used to treat hypercalcemia and other disorders caused by cancer or calciferol-resistance. In an example, a monoclonal **antibody** recognizing PTRP was produced by hybridoma **23 - 57 - 137 - 1** (FERM BP-5631). mRNA from this cell culture was used to produce cDNA from which DNA coding for the mouse V region CDR of H and L chains was isolated. DNA coding for a humanized **antibody** was assembled using this mouse DNA and human DNA for the other regions obtained from the preferred sources. It was inserted into vector plasmid pUC19 and expressed in CHO and COS cells to give humanized **antibody** . (182pp)

L13 ANSWER 4 OF 5 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 1998-06396 BIOTECHDS
TITLE: Chimeric and humanized antibodies against human parathormone-related peptides;
chimeric antibody, humanized antibody and monoclonal antibody production by vector plasmid pUC19 expression in CHO and COS cell and hybridoma cell culture for hypercalcemia therapy
AUTHOR: Sato K; Wakahara Y; Yabuta N
PATENT ASSIGNEE: Chugai
LOCATION: Tokyo, Japan.
PATENT INFO: WO 9813388 2 Apr 1998
APPLICATION INFO: WO 1997-JP3382 24 Sep 1997
PRIORITY INFO: JP 1996-214168 24 Jul 1996; JP 1996-255196 26 Sep 1996
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: WPI: 1998-230640 [20]
AN 1998-06396 BIOTECHDS
AB Humanized and chimeric antibodies which recognize human parathormone-related peptides (PTRP) are new and contain chimeric L and/or H chains in which the C region is of human origin and the L region is of mouse origin. Preferably, the V region is humanized containing framework regions of human origin and complementarity determining regions (CDRs) of mouse origin. Also claimed is: DNA coding for the antibody and its component parts; vectors containing the DNA; transformant hosts containing the vectors; and antibody production by transformant culture. The above may be used to treat hypercalcemia and other disorders caused by cancer or calciferol-resistance. In an example, a monoclonal antibody recognizing PTRP was produced by hybridoma **23-57-137**-1 (FERM BP-5631). mRNA from this cell culture was used to produce cDNA from which DNA coding for the mouse V region CDR of H and L chains was isolated. DNA coding for a humanized antibody was assembled using this mouse DNA and human DNA for the other regions obtained from the preferred sources. It was inserted into vector plasmid pUC19 and expressed in CHO and COS cells to give humanized antibody. (182pp)

HHM. Recently, a PTH-related protein (PTHrP) has been shown to be responsible for the hypercalcemia in the syndrome of HHM. In the present study we evaluated the effects of a neutralizing antiserum to PTHrP on bone histomorphometric parameters in hypercalcemic athymic mice bearing a **human** squamous cell lung **cancer** . These effects were compared to those of **tumor** resection. Similar to the effects of **tumor** resection, the antiserum to PTHrP resulted in a decrease in serum Ca levels, a decrease in bone resorption, and an increase in bone formation parameters. The studies, therefore, indicate that PTHrP is the major factor responsible for all of the features, including the decreased bone formation seen in HHM.

**29/3,AB/78 (Item 78 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

05787228 89034877 PMID: 2846659
**Antibodies to** parathyroid hormone - related protein **lower serum calcium in athymic mouse models of** malignancy **-associated hypercalcemia due to** human tumors .
Kukreja SC; Shevrin DH; Wimbiscus SA; Ebeling PR; Danks JA; Rodda CP; Wood WI; Martin TJ
Department of Medicine, Veterans Administration West Side, Chicago, Illinois 60612.
Journal of clinical investigation (UNITED STATES) Nov 1988, 82 (5) p1798-802, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A parathyroid hormone-related protein (PTHrP) has recently been isolated from **tumors** associated with hypercalcemia. In the present study, we tested the effects of neutralizing antisera to the PTHrP on serum calcium and urine cAMP in two animal models of **malignancy** -associated hypercalcemia. The animal models consisted of (a) a **human** squamous cell lung **cancer** and (b) a **human** laryngeal **cancer** , both serially carried in athymic mice. The antisera specifically reduced the elevated serum calcium and urinary cAMP levels in the **tumor** -bearing animals. We conclude that PTHrP plays a major role in the pathogenesis of **malignancy** -associated hypercalcemia.

**29/3,AB/80 (Item 80 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

05439982 90048075 PMID: 2682846
**Parathyroid hormone-related protein: isolation, molecular cloning, and mechanism of action.**
Martin TJ; Allan EH; Caple IW; Care AD; Danks JA; Diefenbach-Jagger H; Ebeling PR; Gillespie MT; Hammonds G; Heath JA; et al
Recent progress in hormone research (UNITED STATES) 1989, 45 p467-502; discussion 502-6, ISSN 0079-9963 Journal Code: R1D
Languages: ENGLISH
Document type: Journal Article; Review; Review, Academic
Record type: Completed
Many factors, such as interleukin 1, TGF alpha, **tumor** necrosis factor alpha and beta, and PGs, have been implicated in etiological roles in HHM (Martin and Mundy, 1987). Much interest in the past has also centered upon the likelihood of ectopic secretion of PTH in this condition. We have purified a protein ( **PTHrP** ) implicated in HHM from a **human** lung **cancer** cell line (BEN). Full-length cDNA clones have been isolated and were found to encode a prepropeptide of 36 amino acids and a mature protein of 141 amino acids. Eight of the first 13 amino acids were identical with **human** PTH, although antisera directed to the NH2 terminus of **PTHrP** do not recognize PTH; this homology is not maintained in the remainder of the molecule. **PTHrP** therefore represents a previously unrecognized hormone, possibly related to the PTH gene by a gene duplication mechanism. In support of this notion, the **PTHrP** gene has been localized to the short

arm of chromosome 12; it is believed that chromosome 11, containing the PTH gene, and chromosome 12 are evolutionarily related. In addition, the **human PTHrP** gene has been isolated, characterized, and shown to have a similar intron--exon organization as the PTH gene. It is possible that the original ancestral gene is indeed the **PTHrP** gene; resolution of this question awaits studies in lower species. Peptides synthesized to the predicted protein sequence have enabled detailed structure-function studies that have identified NH 2-terminal sequences to be responsible for the biological effects of the molecule. **Antibodies** raised against the various synthetic peptides have led to the immunohistochemical localization of **PTHrP** in many **human** squamous cell carcinomas as well as in a subpopulation of keratinocytes of normal skin. The availability of these **antibodies** has opened the way for the development of a radioimmunoassay to detect **PTHrP** in the sera of **cancer** patients at risk of developing hypercalcemia. The recent characterization of **PTHrP** -like activity in the ovine fetus suggests some physiological function for **PTHrP** . It is possible that **PTHrP** , as the fetal counterpart of PTH, has the role of maintaining the maternal-fetal calcium gradient. The isolation and characterization of **PTHrP** have added to our understanding of the mechanisms of hypercalcemia and may contribute to the understanding of other metabolic bone diseases, such as osteoporosis and Paget's disease. Finally, and perhaps most importantly, **PTHrP** may play a hitherto unrecognized role in normal cell physiology.

**29/3,AB/86 (Item 5 from file: 5)**
DIALOG(R)File 5:Biosis Previews(R)


07786155 BIOSIS NO.: 000041072106
**PRODUCTION AND CHARACTERIZATION OF MONOCLONAL** ANTIBODIES **TO** PARATHYROID HORMONE - RELATED PROTEIN **37-67**
AUTHOR: HUGHES S J; EMLY J; HUGHES S; RATCLIFFE W A
AUTHOR ADDRESS: WOLFSON RES. LAB., QUEEN ELIZABETH MED. CENTER, BIRMINGHAM B15 2TH, UK.
JOURNAL: 10TH JOINT MEETING OF BRITISH ENDOCRINE SOCIETIES, BRIGHTON, ENGLAND, UK, APRIL 15-18, 1991. J ENDOCRINOL 129 (SUPPL.). 1991. ABSTRACT 119. 1991
CODEN: JOENA
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1991

**29/3,AB/88 (Item 7 from file: 5)**
DIALOG(R)File 5:Biosis Previews(R)


06459570 BIOSIS NO.: 000037031581
**EFFECT OF** ANTIBODIES **TO** PARATHYROID HORMONE - RELATED PROTEIN **ON BONE HISTOMORPHOMETRY IN HYPERCALCEMIA OF** MALIGNANCY
AUTHOR: KUKREJA S C; ROSOL T J; WIMBISCUS S A; SHEVRIN D H; BARENGOLTS E I; MARTIN T J
AUTHOR ADDRESS: VA WEST SIDE, CHICAGO, ILL.
JOURNAL: NATIONAL MEETING OF THE AMERICAN FEDERATION FOR CLINICAL RESEARCH, WASHINGTON, D.C., USA, APRIL 28-MAY 1, 1989. CLIN RES 37 (2). 1989. 454A. 1989
CODEN: CLREA
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1989

**29/3,AB/99 (Item 10 from file: 34)**

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci


01450021 Genuine Article#: HA120 Number of References: 26
**Title: PRODUCTION AND CHARACTERIZATION OF MONOCLONAL-ANTIBODIES TO THE MID-REGION 37-67 SEQUENCE OF** PARATHYROID HORMONE - RELATED PROTEIN (Abstract Available)
Author(s): RATCLIFFE WA; BOWDEN SJ; EMLY J; HUGHES S; RATCLIFFE JG
Corporate Source: QUEEN ELIZABETH MED CTR,DEPT CLIN CHEM,WOLFSON RES LABS/BIRMINGHAM B15 2TH/W MIDLANDS/ENGLAND/
Journal: JOURNAL OF IMMUNOLOGICAL METHODS, 1992, V146, N1 (JAN 21), P33-42
Language: ENGLISH Document Type: ARTICLE
Abstract: The production and characterisation of monoclonal antibodies (MAb) to the mid-region sequence 37-67 of **human parathyroid hormone - related protein** ( **PTHRP** ) is described. In spite of the poor immunogenicity of this sub-fragment of **PTHRP** . a high percentage of specific hybrids were produced by boosting with conjugate and free peptide prior to cell fusion. Seven of the MAbs produced cross-reacted with PTHRP37-67, PTHRP1-86 and native forms of **PTHRP** . Inhibition studies with peptide sub-fragments of PTHRP37-67 indicated that the majority recognised the 45-59 region. In a RIA for PTHRP1-86, detection limits ranged from 0.17 to 0.9 ng PTHRP1-86/tube, and no cross-reaction was found with PTH1-84. Two MAbs 1D11 and 4B10 were shown to be of potential use in measuring PTHRP1-86 in a two-site immunoradiometric assay in combination with either a solid phase consisting of a MAb to PTHRP1-34, or iodinated affinity purified rabbit **antibodies** to PTHRP1-34. MAb 1D11 coupled to Sepharose was suitable for immunoextraction of **PTHRP** , and successfully localised **PTHRP** on immunoblots. Two additional MAbs were produced which recognised an epitope unique to PTHRP37-67 located in the 37-46 region of the peptide.

**29/3,AB/113 (Item 9 from file: 94)**
DIALOG(R)File 94:JICST-EPlus


00706210 JICST ACCESSION NUMBER: 88A0581464 FILE SEGMENT: JICST-E
Malignancy **-associated hypercalcemia: Pathogenesis and treatment.**
SATO KANJI (1)
(1) Tokyo Women's Medical College, School of Medicine, Inst. of Clinical Endocrinology
Tokyo Joshi Ika Daigaku Zasshi(Journal of Tokyo Women's Medical College), 1988, VOL.58,NO.9, PAGE.939-946, FIG.4, TBL.1, REF.34
JOURNAL NUMBER: G0684AAY ISSN NO: 0040-9022 CODEN: TJIZA
UNIVERSAL DECIMAL CLASSIFICATION: 616-006-071 616.39
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Review article
MEDIA TYPE: Printed Publication
ABSTRACT: **Malignancy** -associated hypercalcemia(MAH) is the most frequent disorder in patients with hypercalcemia. Previously, it was postulated that most of MAH was due to bone metastasis. However, it was recently elucidated that MAH is humorally mediated in a majority of cases. Hypercalcemia-producing factors produced by **tumor** cells are bone-resorbing factors in vitro and an increasing number of bone-resorbing factors are being reported. Potential mediators for MAH are **parathyroid hormone - related protein** (PTH-rP), interleukin 1 .ALPHA. and .BETA., **tumor** necrosis factor .ALPHA. and .BETA., or active vitamin D metabolites. Some **tumor** cells established from patients with marked hypercalcemia produce two bone-resorbing factors. The best treatment for MAH is, of cause, total resection of a **tumor** producing bone-resorbing factors. If surgical procedure is not indicated, medical treatment such as saline infusion, administration of calcitonin and glucocorticoid can ameliorate hypercalcemia in most instances. However, these medical procedure is non-specific treatment

and the effect is only temporary in most cases. Now that humoral mediators responsible for MAH have been elucidated, specific treatment of MAH, such as administration of anti-PTH-rP **antibody** , will be developed in the near future.(author abst.)

**29/3,AB/115 (Item 1 from file: 357)**
DIALOG(R)File 357:Derwent Biotech Resource
(c) 2002 Derwent Info & ISI. All rts. reserv.

0073809 DBA Accession No.: 88-04658 PATENT
**Purified parathormone related hormone - purification from BEN cell culture and useful for preparing antibodies**
PATENT ASSIGNEE: Univ.Melbourne 1988
PATENT NUMBER: WO 8800596 PATENT DATE: 880128 WPI ACCESSION NO.: 88-036432 (8805)
PRIORITY APPLIC. NO.: AU 87349 APPLIC. DATE: 870213
NATIONAL APPLIC. NO.: WO 87AU16 APPLIC. DATE: 8706045
LANGUAGE: English
ABSTRACT: Pure parathormone related hormone ( **PTHrP** ) is new and **antibody** reagents capable of binding to epitopes of **PTHrP** are claimed. The following modified subunits of **PTHrP** are also new: (Glu8, Asn10, Cys11) **PTHrP** (1-1), (Asn10) **PTHrP** (1-16), and (Asn10, Tyr17) **PTHrP** (1-17). The purified **PTHrP** is obtained by: (a) culturing BEN cells (originally established from a hypercalcemic patient with a squamous cell carcinoma of the bronchus); (b) applying the culture medium to a cation exchange resin; (c) eluting fractions and assaying for **PTHrP** activity; and (d) performing HPLC on those fractions possessing **PTHrP** activity. **PTHrP** is active in humoral hypercalcemia of **malignancy** . Its precise role may now be characterized using the purified **PTHrP** , which may also be used to produce **antibodies** . The **antibodies** may be used to detect **PTHrP** activity and as a diagnostic aid to detect **cancers** , chronic renal failure and other bone diseases in which parathormone plays a role. The **antibodies** may also be useful as immunohistochemical diagnostic reagents for immunolocalization of cells capable of producing **PTHrP** in various tissues. (51pp)

**29/3,AB/116 (Item 1 from file: 399)**
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

**128293971 CA: 128(24)293971d PATENT**
**Antibody against human parathormone related peptides**
INVENTOR(AUTHOR): Sato, Kou; Wakahara, Yuji; Yabuta, Naohiro
LOCATION: Japan,
ASSIGNEE: Chugai Seiyaku K. K.; Sato, Kou; Wakahara, Yuji; Yabuta, Naohiro
PATENT: PCT International ; WO 9813388 A1 DATE: 19980402
APPLICATION: WO 97JP3382 (19970924) *JP 96255196 (19960926) *JP 97214168 (19970724)
PAGES: 184 pp. CODEN: PIXXD2 LANGUAGE: Japanese CLASS: C07K-016/18A; C07K-016/46B; C12N-015/13B; C12N-015/62B; C12N-005/16B; C12P-021/02B; C12P-021/08B; A61K-039/395B; C12P-021/02B; C12R-001/91B; C12P-021/08B; C12R-001/91B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; KE; KG; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; KE; LS; MW; SD ; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG

**29/3,AB/123 (Item 2 from file: 654)**
DIALOG(R)File 654:US PAT.FULL.
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02644879
Utility
METHOD TO AMELIORATE OSTEOLYSIS AND METASTASIS
[Administering antibodies specific to **parathyroid hormone - related protein** ]

PATENT NO.: 5,626,845
ISSUED: May 06, 1997 (19970506)
INVENTOR(s): Yoneda, Toshiyuki, San Antonio, TX (Texas), US (United States of America)
Mundy, Gregory R., San Antonio, TX (Texas), US (United States of America)
ASSIGNEE(s): Xenotech Incorporated, (A U.S. Company or Corporation), Foster City, CA (California), US (United States of America)
[Assignee Code(s): 41818]
APPL. NO.: 8-376,359
FILED: January 23, 1995 (19950123)

FULL TEXT: 442 lines

ABSTRACT
Materials immunoreactive with **parathyroid hormone - related protein** (PTH-rp) are used in the invention method to prevent and treat metastasis and **cancer** cell growth in bone as well as osteolysis and symptomatic sequelae thereof. **Humanized antibodies** are included in the invention for application of the invention method to **human** subjects.
?

**36/3,AB/1 (Item 1 from file: 357)**
DIALOG(R)File 357:Derwent Biotech Resource


0224799 DBA Accession No.: 98-06396 PATENT
**Chimeric and humanized** antibodies **against human parathormone-related peptides - chimeric** antibody , **humanized** antibody **and monoclonal** antibody **production by vector plasmid pUC19 expression in CHO and COS cell and hybridoma cell culture for hypercalcemia therapy**
AUTHOR: Sato K; Wakahara Y; Yabuta N
CORPORATE SOURCE: Tokyo, Japan.
PATENT ASSIGNEE: Chugai 1998
PATENT NUMBER: WO 9813388 PATENT DATE: 980402 WPI ACCESSION NO.: 98-230640 (9820)
PRIORITY APPLIC. NO.: JP 96214168 APPLIC. DATE: 960724
NATIONAL APPLIC. NO.: WO 97JP3382 APPLIC. DATE: 970924
LANGUAGE: JA
ABSTRACT: Humanized and chimeric **antibodies** which recognize human parathormone-related peptides (PTRP) are new and contain chimeric L and/or H chains in which the C region is of human origin and the L region is of mouse origin. Preferably, the V region is humanized containing framework regions of human origin and complementarity determining regions (CDRs) of mouse origin. Also claimed is: DNA coding for the **antibody** and its component parts; vectors containing the DNA; transformant hosts containing the vectors; and **antibody** production by transformant culture. The above may be used to treat hypercalcemia and other disorders caused by cancer or calciferol-resistance. In an example, a monoclonal **antibody** recognizing PTRP was produced by hybridoma **23 - 57 - 137 - 1** (FERM BP-5631). mRNA from this cell culture was used to produce cDNA from which DNA coding for the mouse V region CDR of H and L chains was isolated. DNA coding for a humanized **antibody** was assembled using this mouse DNA and human DNA for the other regions obtained from the preferred sources. It was inserted into vector plasmid pUC19 and expressed in CHO and COS cells to give humanized **antibody** . (182pp)

**36/3,AB/2 (Item 1 from file: 399)**
DIALOG(R)File 399:CA SEARCH(R)


**130010622 CA: 130(2)10622w PATENT**
**Antibody to parathyroid hormone-related peptide (PTHrP) or the PTHrP receptor antagonist as a cancerous cachexia remedy**
INVENTOR(AUTHOR): Sato, Koh; Tunenari, Toshiaki; Ishii, Kimie
LOCATION: Japan,
ASSIGNEE: Chugai Seiyaku Kabushiki Kaisha
PATENT: PCT International ; WO 9851329 A1 DATE: 19981119
APPLICATION: WO 98JP2116 (19980513) *JP 97125505 (19970515) *JP 97194445 (19970718)
PAGES: 125 pp. CODEN: PIXXD2 LANGUAGE: Japanese CLASS: A61K-038/29A; A61K-039/395B; A61K-045/00B; C12N-015/13B; C12P-021/02B; C12P-021/08B; C07K-016/26B; C07K-016/28B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; GW; HU; ID; IL; IS; KE; KG; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
?